

## MEGACE ES - megestrol acetate suspension

Megace ES

### DESCRIPTION

Megace® ES (megestrol acetate) oral suspension contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone. Megestrol acetate is a white, crystalline solid chemically designated as 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate. Solubility at 37° C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. Its molecular weight is 384.52.

The chemical formula is C<sub>24</sub>H<sub>32</sub>O<sub>4</sub> and the structural formula is represented as follows:

Megace® ES (megestrol acetate) is a concentrated formula supplied as an oral suspension containing 125 mg of megestrol acetate per mL.

Megace® ES (megestrol acetate) oral suspension contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, hydroxypropyl methylcellulose (hypromellose), natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.

### CLINICAL PHARMACOLOGY

There are several analytical methods used to estimate megestrol acetate plasma concentrations, including gas chromatography-mass fragmentography (GC-MF), high pressure liquid chromatography (HPLC) and radioimmunoassay (RIA). The GC-MF and HPLC methods are specific for megestrol acetate and yield equivalent concentrations. The RIA method reacts to megestrol acetate metabolites and is, therefore, non-specific and indicates higher concentrations than the GC-MF and HPLC methods. Plasma concentrations are dependent, not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet and liver function.

#### Mechanism of Action

Several investigators have reported on the appetite enhancing property of megestrol acetate and its possible use in cachexia. The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at the present time.

#### Pharmacokinetic Properties:

Plasma concentrations of megestrol acetate after administration of 625 mg (125 mg/mL) of Megace® ES oral suspension are equivalent under fed conditions to 800 mg (40 mg/mL) of megestrol acetate oral suspension (see figure below).

#### Mean plasma concentrations of megestrol acetate after oral administration of 625 mg of Megace® ES (megestrol acetate) oral suspension and 800 mg of megestrol acetate oral suspension to healthy volunteers under fed conditions

In order to characterize the dose proportionality of Megace® ES, pharmacokinetic studies across a range of doses were conducted when administered under fasting and fed conditions. Pharmacokinetics of megestrol was linear in the dosing range between 150 mg and 675 mg after Megace® ES administration regardless of meal condition. The C<sub>max</sub> and AUC under a high fat meal were increased by 48% and 36%, respectively, compared to those under the fasting after 625 mg Megace® ES administration (Table 1). However, a high fat meal significantly increased AUC and C<sub>max</sub> of megestrol to 2-fold and 7-fold, respectively, compared to those under fasting condition after administration of 800 mg in the original formulation. There was no difference in safety following administration in the fed state, therefore Megace® ES could be taken without regard to meals.

*megestrol acetate oral suspension																
Table 1 - Pharmacokinetic Studies Conducted with Megace® ES																
Amount Dosed	150 mg	250 mg	375 mg	450 mg	575 mg	625 mg	675 mg	800 mg*								
Dose	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL	20 mL								
	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed	Fast	Fed
C <sub>max</sub> (ng/mL)	412	379	647	588	810	958	955	1079	-	1421	1133	1618	1044	1616	187	1364
AUC <sub>0-∞</sub> (ng·h/mL)	3058	3889	5194	6328	7238	12193	9483	11800	-	14743	12095	16268	11879	17029	8942	18625

Tmax (h)	1.74	3.80	1.58	3.38	1.56	3.42	1.74	3.16	-	3.75	1.72	2.91	1.96	2.76	5.89	3.85
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Plasma steady state pharmacokinetics of megestrol acetate were evaluated in 10 adult, cachectic male patients with acquired immunodeficiency syndrome (AIDS) and an involuntary weight loss greater than 10% of baseline. Patients received single oral doses of 800 mg/day of megestrol acetate oral suspension for 21 days. Plasma concentration data obtained on day 21 were evaluated for up to 48 hours past the last dose.

Mean ( $\pm$ 1SD) peak plasma concentration (C<sub>max</sub>) of megestrol acetate was 753 ( $\pm$ 539) ng/mL. Mean area under the concentration time-curve (AUC) was 10476 ( $\pm$ 7788) ng x hr/mL. Median T<sub>max</sub> value was five hours. Seven of 10 patients gained weight in three weeks.

Additionally, 24 adult, asymptomatic HIV seropositive male subjects were dosed once daily with 750 mg of megestrol acetate oral suspension. The treatment was administered for 14 days. Mean C<sub>max</sub> and AUC values were 490 ( $\pm$ 238) ng/mL and 6779 ( $\pm$ 3048) hr x ng/mL, respectively. The median T<sub>max</sub> value was three hours. The mean C<sub>max</sub> value was 202 ( $\pm$ 101) ng/mL. The mean % of fluctuation value was 107 ( $\pm$ 40).

#### Metabolism

Megestrol acetate metabolites which were identified in urine constituted 5% to 8% of the dose administered. Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in urine and feces.

#### Elimination

The major route of drug elimination in humans is urine. When radiolabeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5% to 78.4% (mean 66.4%) and fecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%).

#### Special Populations

The pharmacokinetics of megestrol acetate has not been studied in any special populations.

#### INDICATIONS AND USAGE

Megace<sup>®</sup> ES (megestrol acetate) oral suspension is indicated for the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS).

#### CONTRAINDICATIONS

History of hypersensitivity to megestrol acetate or any component of the formulation. Known or suspected pregnancy

#### WARNINGS

Megestrol acetate may cause fetal harm when administered to a pregnant woman. For animal data on fetal effects, (see

**PRECAUTIONS: Impairment of Fertility** section). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Megestrol acetate is not intended for prophylactic use to avoid weight loss.

(See also **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility** section).

The glucocorticoid activity of megestrol acetate oral suspension has not been fully evaluated. Clinical cases of new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushing's Syndrome have been reported in association with the chronic use of megestrol acetate. In addition, clinical cases of adrenal insufficiency have been observed in patients receiving or being withdrawn from chronic megestrol acetate therapy in the stressed and non-stressed state. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic pituitary-adrenal suppression in patients treated with chronic megestrol acetate therapy. Therefore, the possibility of adrenal insufficiency should be considered in any patient receiving or being withdrawn from chronic Megace<sup>®</sup> ES therapy who presents with symptoms and/or signs suggestive of hypoadrenalism (e.g., hypotension, nausea, vomiting, dizziness, or weakness) in either the stressed or non-stressed state. Laboratory evaluation for adrenal insufficiency and consideration of replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death. Finally, in patients who are receiving or being withdrawn from chronic Megace<sup>®</sup> ES therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid during stress or serious intercurrent illness (e.g., surgery, infection).

#### GENERAL PRECAUTIONS

Therapy with Megace<sup>®</sup> ES (megestrol acetate) oral suspension for weight loss should only be instituted after treatable causes of weight loss are sought and addressed. These treatable causes include possible malignancies, systemic infections, gastrointestinal disorders affecting absorption, endocrine disease and renal or psychiatric diseases.

Effects on HIV viral replication have not been determined.

Use with caution in patients with a history of thromboembolic disease.

#### Use in Diabetics

Exacerbation of pre-existing diabetes with increased insulin requirements have been reported in association with the use of megestrol acetate.

#### Information for Patients

Patients using Megace<sup>®</sup> ES (megestrol acetate) should receive the following instructions:

1. This medication is to be used as directed by the physician.

2. Megace® ES (625 mg/5 mL) does not contain the same amount of megestrol acetate as Megace® oral suspension or any of the other megestrol acetate oral suspensions. Megace® ES contains 625 mg of megestrol acetate per 5 mL whereas Megace® oral suspension and other megestrol acetate oral suspensions contain 800 mg per 20 mL.
3. **The prescriber should inform the patient about the product differences to avoid overdosing or underdosing of megestrol acetate. The recommended adult dosage of Megace® ES is one teaspoon (5 mL) once a day. Please see table in DOSAGE AND ADMINISTRATION section.**
4. Report any adverse reaction experiences while taking this medication.
5. Use contraception while taking this medication if you are a woman capable of becoming pregnant.
6. Notify your physician if you become pregnant while taking this medication.

#### Drug Interactions

Pharmacokinetic studies show that there are no significant alterations in pharmacokinetic parameters of zidovudine or rifabutin to warrant dosage adjustment when megestrol acetate is administered with these drugs. A pharmacokinetic study demonstrated that coadministration of megestrol acetate and indinavir results in a significant decrease in the pharmacokinetic parameters (~36% for C<sub>max</sub> and ~28% for AUC) of indinavir. Administration of a higher dose of indinavir should be considered when coadministering with megestrol acetate. The effects of indinavir, zidovudine or rifabutin on the pharmacokinetics of megestrol acetate were not studied.

#### Carcinogenesis and Mutagenesis and Impairment of Fertility

Data on carcinogenesis were obtained from studies conducted in dogs, monkeys and rats treated with megestrol acetate at doses 53.2, 26.6 and 1.3 times lower than the proposed dose (13.3 mg/kg/day) for humans. No males were used in the dog and monkey studies. In female beagles, megestrol acetate (0.01, 0.1 or 0.25 mg/kg/day) administered for up to 7 years induced both benign and malignant tumors of the breast. In female monkeys, no tumors were found following 10 years of treatment with 0.01, 0.1 or 0.5 mg/kg/day megestrol acetate. Pituitary tumors were observed in female rats treated with 3.9 or 10 mg/kg/day of megestrol acetate for 2 years. The relationship of these tumors in rats and dogs to humans is unknown but should be considered in assessing the risk-to-benefit ratio when prescribing Megace® ES (megestrol acetate) oral suspension and in surveillance of patients on therapy. (See **WARNINGS** section).

#### Mutagenesis

No mutagenesis data are currently available.

#### Impairment of Fertility

Perinatal/postnatal (segment III) toxicity studies were performed in rats at doses (0.05 to 12.5 mg/kg) *less* than that indicated for humans (13.3 mg/kg); in these low dose studies, the reproductive capability of male offspring of megestrol acetate-treated females was impaired. Similar results were obtained in dogs. Pregnant rats treated with megestrol acetate showed a reduction in fetal weight and number of live births, and feminization of male fetuses. No toxicity data are currently available on male reproduction (spermatogenesis).

#### Pregnancy

**Pregnancy Category X.** (See **WARNINGS** and **PRECAUTIONS: Impairment of Fertility** sections). No adequate animal teratology information is available at clinically relevant doses.

#### Nursing Mothers

Because of the potential for adverse effects on the newborn, nursing should be discontinued if Megace® ES (megestrol acetate) oral suspension is required.

#### Use in HIV Infected Women

Although megestrol acetate has been used extensively in women for the treatment of endometrial and breast cancers, its use in HIV infected women has been limited.

All 10 women in the clinical trials reported breakthrough bleeding.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### Geriatric Use

Clinical studies of megestrol acetate oral suspension in the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with AIDS did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Megestrol acetate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

#### ADVERSE REACTIONS

## Clinical Adverse Events

Adverse events which occurred in at least 5% of patients in any arm of the two clinical efficacy trials and the open trial are listed below by treatment group. All patients listed had at least one post baseline visit during the 12 study weeks. These adverse events should be considered by the physician when prescribing Megace<sup>®</sup> ES (megestrol acetate) oral suspension.

ADVERSE EVENTS% of Patients Reporting							
			Open				
	Trial 1 (N=236)	Trial 2 (N=87)	Label Trial				
Megestrol Acetate,	Placebo				Placebo		
mg/day	0	100	400	800	0	800	1200
No. of Patients	N=34	N=68	N=69	N=65	N=38	N=49	N=176
Diarrhea	15	13	8	15	8	6	10
Impotence	3	4	6	14	0	4	7
Rash	9	9	4	12	3	2	6
Flatulence	9	0	1	9	3	10	6
Hypertension	0	0	0	8	0	0	4
Asthenia	3	2	3	6	8	4	5
Insomnia	0	3	4	6	0	0	1
Nausea	9	4	0	5	3	4	5
Anemia	6	3	3	5	0	0	0
Fever	3	6	4	5	3	2	1
Libido Decreased	3	4	0	5	0	2	1
Dyspepsia	0	0	3	3	5	4	2
Hyperglycemia	3	0	6	3	0	0	3
Headache	6	10	1	3	3	0	3
Pain	6	0	0	2	5	6	4
Vomiting	9	3	0	2	3	6	4
Pneumonia	6	2	0	2	3	0	1
Urinary Frequency	0	0	1	2	5	2	1

Adverse events which occurred in 1% to 3% of all patients enrolled in the two clinical efficacy trials with at least one follow-up visit during the first 12 weeks of the study are listed below by body system. Adverse events occurring less than 1% are not included. There were no significant differences between incidence of these events in patients treated with megestrol acetate and patients treated with placebo.

Body as a Whole - abdominal pain, chest pain, infection, moniliasis and sarcoma

Cardiovascular System - cardiomyopathy and palpitation

Digestive System - constipation, dry mouth, hepatomegaly, increased salivation and oral moniliasis

Hemic and Lymphatic System - leukopenia

Metabolic and Nutritional - LDH increased, edema and peripheral edema

Nervous System - paresthesia, confusion, convulsion, depression, neuropathy, hypesthesia and abnormal thinking

Respiratory System - dyspnea, cough, pharyngitis and lung disorder

Skin and Appendages - alopecia, herpes, pruritus, vesiculobullous rash, sweating and skin disorder

Special Senses - amblyopia

Urogenital System - albuminuria, urinary incontinence, urinary tract infection and gynecomastia

Postmarketing

Postmarketing reports associated with megestrol acetate oral suspension include thromboembolic phenomena including thrombophlebitis, deep vein thrombosis, and pulmonary embolism; and glucose intolerance (see **WARNINGS** and **PRECAUTIONS** sections).

**OVERDOSAGE**

No serious unexpected side effects have resulted from studies involving megestrol acetate oral suspension administered in dosages as high as 1200 mg/day. Megestrol acetate has not been tested for dialyzability; however, due to its low solubility it is postulated that dialysis would not be an effective means of treating overdose.

#### DOSAGE AND ADMINISTRATION

The recommended adult initial dosage of Megace<sup>®</sup> ES (megestrol acetate) oral suspension is 625 mg/day (5 mL/day or one teaspoon daily). **Please refer to the table below for correct dosing and administration.** Shake container well before using.

<b>PRODUCT DIFFERENCES</b>		
	Megace <sup>®</sup> ES Oral Suspension	Megace <sup>®</sup> and other megestrol acetate oral suspensions
mg/mL	125 mg/mL	40 mg/mL
Recommended Daily Dose	625 mg	800 mg
Daily Volume Intake	5 mL (teaspoon)	20 mL (dosing cup)
Formulation	Concentrated formula	Regular formula

In clinical trials evaluating different dose schedules, daily doses of 400 and 800 mg/day of megestrol acetate oral suspension (800 mg/20 mL equivalent to 625 mg/5 mL of Megace<sup>®</sup> ES formula) were found to be clinically effective.

#### HOW SUPPLIED

Megace<sup>®</sup> ES (megestrol acetate) oral suspension is a concentrated formula available as a milky white, lemon-lime flavored oral suspension containing 125 mg of megestrol acetate per mL.

NDC 49884-949-69	Bottles of 150 mL (5 fl. oz.)
NDC 49884-949-52	Unit of Use Bottles of 5 mL (0.17 fl. oz.) - Institutional Use Only

#### STORAGE

Store Megace<sup>®</sup> ES (megestrol acetate) oral suspension between 15° to 25° C (59° to 77° F) and dispense in a tight container. Protect from heat.

megaceessusp

Packaged and distributed by:

Gainesville, GA 30501

**Megace ES**  
**625mg/5mL 150 mL**

Generic For:  
**NDC 16590-254-33**

Each mL Contains: 125mg of Megestrol acetate (Oral Suspension)

Mfg By: Par Pharmaceutical Co., Inc.  
Spring Valley, NY 10977

Mfg Lot: 21844302  
Discard After: 04/12

NDC 49884-949-69  
MD 11/25/2009 9625772

**RX ONLY-KEEP OUT OF REACH OF CHILDREN**

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.  
**Could cause Dizziness, weakness, Nausea, Blurred vision and vomiting**


16590-254-33